REMARKS

In view of the above amendments and the following remarks, reconsideration and further examination are respectfully requested.

Status of All of the Claims

Below is the status of the claims in this application.

1. Claim(s) pending: 24-58.
2. Claim(s) canceled: 1-23.
3. Claim(s) added: 24-58.
4. Claims withdrawn from consideration but not canceled: None.

The new claims generally comprising a reorganization of the prior pending claims, and as such they are supported on the same bases as were the prior pending claims. The claims have been submitted as new claims in order to have the claims presented in a more orderly fashion for the convenience of the examination of this application.

Rejections Under §112

Claims 6-15 were rejected as being indefinite for failing to particularly point out and distinctly claim the invention for use of the phrase "at or about". These claims have been canceled, and the rejections are therefore obviated. Further, the new claims in the application do not use the phrase "at or about" and therefore are not subject to this ground of rejection under §112.

Rejections Under §102/103

The claims 1-23 were previously rejected as unpatentable under §102 based on references to DeMeere or Skrabanja, or under §103 based on the combination of DeMeer in view of Skrabanja or Franks. However, claims 1-23 have been canceled and the rejection of those claims

has been obviated. Applicant herein addresses the DeMeere, Skrabanja and Franks references relative to new claims 24-58.

Each of the new claims pending in this application are related to freeze-dried formulations including certain constituents. More specifically, each of the independent claims covers formulations which "consist essentially of" certain components, including FSH, LH and identified excipients. It has been found that such formulations provide surprising stability to the FSH/LH preparations, without the need for yet additional components.

DeMeere

The DeMeere patent '132 has been cited as showing lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer, as well as other constituents. While DeMeere does disclose a variety of information relating to FSH and/or LH formulations, it does not teach or suggest the present invention. In particular, DeMeere emphasizes the need for the dicarboxylic acid salt stabilizer in order to achieve a suitably stable formulation.

DeMeere indicates that stability is a problem for gonadotropin formulations, especially those which include more than one gonadotropin:

> "A need exists for a gonadotropin containing pharmaceutical preparation which is stable over a sufficiently long period of time for the product to be manufactured, shipped, and stored prior to use. The need is especially great for a stable preparation containing more than one gonadotropin." Col. 1, lines 38-43.

DeMeere further indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "Recently however, with the advent of more effective production and purification techniques, preparations of certain very pure gonadotropins are insufficiently stable. They degrade in a relatively short time, losing activity. In order to prevent or slow down this degradation, attempts were made to freeze-dry

(lyophilize) the preparations. Lyophilization has only been partially successful however." Col. 1, lines 30-37.

"FSH purified from natural sources is generally only partially purified. The impurities seem to act to stabilize it somewhere. With rFSH, however the impurities are not present, and thus the FSH is more susceptible to rapid degradation and freeze-drying losses." Col. 2, lines 53-58.

The solution provided by DeMeere is the use of the salts of dicarboxylic acids to stabilize the formulations:

"Disclosed are lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer." Abstract, lines 1-3.

"Generally, the invention includes a gonadotropin containing lyophilized protein preparation which contains a dicarboxylic acid salt stabilizer. . . . The preparation will contain a sufficient amount of dicarboxylic acid salt to stabilize the gonadotropin in its freeze-dried form for a desired time at a desired temperature." Summary of the Invention, col. 1, lines 46-56.

DeMeere also teaches that formulations without the dicarboxylic acid salts are not stable. In Example I, DeMeere described the preparation of two FSH samples with the difference (other than the concentration of the Tween 20) being that the first sample included sodium citrate and the second did not. The results indicate the instability of FSH in the absence of sodium citrate, stating:

"The first sample is stored for 3 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed little oligomer formation. The second sample, not containing sodium citrate, was stored for 6 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed much more oligomer formation.

The profile of the first sample showed no degradation products while the profile of the second sample showed almost exclusively oligomeric products." Col. 6, lines 45-56.

Similarly, FIG. 2 shows only a 40% recovery of activity of HCG after freeze-drying, and only a 5% recovery of activity after storage at 50°C, in the absence of a citrate salt.

DeMeere thus specifically teaches the need for the dicarboxylic acid salts, e.g., sodium citrate, in order to stabilize the FSH/LH formulations. The formulations may also include other excipients, including non-reducing salts (e.g., sucrose) to increase the "collapse temperature", and anti-adsorption agents (e.g., Polysorbates) to prevent adsorbance of the protein to the container walls. The use of sodium biphosphate is also mentioned. But in each instance, sodium citrate or the like is included.

Skrabanja

Similarly, Skrabanja '945, primarily focused on liquid preparations, describes formulations including FSH, LH and/or other gonadotropins which include dicarboxylic acid salts as stabilizers:

> "The invention relates to a liquid gonadotropin-containing formulation which comprises a gonadotropin and stabilizing amounts of a polycarboxylic acid or a salt thereof and of a thioether compound." Page 3, lines 15-16.

Skrabanja also indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "With recFSH, however the impurities are not present and thus the FSH, being present in comparatively low concentration on the basis of protein is more susceptible to rapid degradation." Page 3, lines 53-54.

While Skrabanja mentions the use of disaccharides, such as sucrose, it does so in the context of formulations which first include the polycarboxylic acid or salt and the thioether:

> "It has been found that the incorporation of a nonreducing disaccharide, such as sucrose or trehalose, into a formulation, which already comprises a polycarboxylic acid, or a salt thereof, and a thioether compound as stabilizers, further increases the stability of the gonadotropin in the liquid formulation." Page 4, lines 16-18 (emphasis added).

Comparison of the Claims and the Cited Art

The claimed invention is directed generally to freeze-dried formulations which include several identified components, namely FSH, LH, a surfactant selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate, a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols, an antioxidant; and a phosphate buffer. More specifically, the invention is limited to formulations which "consist essentially of" these components. By contrast, the cited art requires the presence of a polycarboxylic acid or salt thereof.

A critical issue addressed by this invention is the provision of a freeze-dried formulation of FSH and LH which is stable. The present application, and the cited art, notes the problem in the art of providing FSH and/or LH formulations which are sufficiently stable over time. One approach in the prior art has been to freeze dry the formulations for reconstitution at a time closer to the time of administration. However, it has remained a problem in the art to provide a freeze-dried formulation which itself is sufficiently stable.

DeMeere and Skrabanja both provide the same answer to the problem. Both required the presence of a polycarboxylic acid, or salt thereof, to stabilize the freeze dried preparations. Without it, DeMeere obtained "almost exclusively oligomeric products," which of course are not suitable for treatment purposes.

The pending claims are therefore seen to be readily distinguished over the cited art. Each of claims 24-45 and 50-58 pertains to a formulation "consisting essentially of" identified components. DeMeere and Skrabanja both teach the further inclusion of a polycarboxylic acid or salt thereof. The significance of the present invention is even greater with respect to the

known instability of formulations including both FSH and LH, and of formulations including highly pure, recombinant FSH and LH – as noted in the DeMeere patent.

In addition, claims 46-49 are directed to freeze-dried formulations which "consist of" the identified components. Claim 46 covers formulations consisting of FSH, LH, at least one of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate, a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols, an antioxidant, and a phosphate buffer. Claim 47 relates to formulations consisting of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine, and a phosphate-buffer. Claim 48 is more specifically directed to formulations including: 0.1-10 μg/mg recombinant human follicle-stimulating hormone, 0.1-3 μg/mg recombinant human luteinising hormone, and 0.001-0.1 mg/mg polyoxyethylene (20) sorbitan monolaurate, based on the weight of the formulation. Finally, claim 49 covers formulations in which the relative weight amounts of the components are 12.0 μg of FSH, 3.7 μg of LH, 30.0 mg of sucrose, 0.05 mg of polyoxyethylene (20) sorbitan monolaurate and 0.1 mg of methionine. Such formulations are not taught or suggested by, or other wise made obvious from, the DeMeere and/or Skrabanja.

The Franks reference has been cited for the limited purpose of teaching the use of sealed vials for containing freeze-dried formulations and liquid diluents. Franks does not negate the clear teachings of both DeMeere and Skrabanja to include polycarboxylic acids, or salts thereof, to obtain stable FSH/LH freeze-dried formulations.

It should be understood that the above remarks are not intended to provide an exhaustive basis for patentability or concede the basis for the rejections in the Office Action, but are simply provided to overcome the rejections made in the Office Action in the most expedient fashion. In view of the above amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and an early notice of allowance is earnestly solicited.

If after reviewing this amendment the Examiner feels that any issues remain which must be resolved before the application can be passed to issue, the Examiner is invited to contact the undersigned representative by telephone to resolve such issues.

Respectfully submitted,

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